PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 November 2000 (08.11.00)	
International application No. PCT/CA00/00299	**Applicant's or agent's file reference** 29297-0223
International filing date (day/month/year) 20 March 2000 (20.03.00)	**Priority date** (day/month/year) 18 March 1999 (18.03.99)
Applicant ADAMSON, James, Gordon et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 October 2000 (17.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
29297-0223		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00299	20/03/2000	18/03/1999
Applicant		
HEMOSOL INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Ir. Application No
PCT/CA 00/00299

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 532 352 A (PLIURA DIANA ET AL) 2 July 1996 (1996-07-02) claims 1-4,7 ---	1-32
P,X	WO 99 56723 A (HEMOSOL INC) 11 November 1999 (1999-11-11) page 9, line 26; claims ---	1-32
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Berte, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Application No
PCT/CA 00/00299

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL HSIA J.C. ET AL: "Pharmacokinetic studies in the rat on a o-raffinose polymerized human hemoglobin." retrieved from STN Database accession no. 92299803 XP002140429 abstract & BIOMATERIALS, ARTIFICIAL CELLS, AND IMMOBILIZATION BIOTECHNOLOGY, (1992) 20/2-4 (587-595). ,	
X	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL MORDENTE A. ET AL: "Antioxidant properties of 2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl) - 1,4-benzoquinone (idebenone)." retrieved from STN Database accession no. 1998044603 XP002140430	1
Y	abstract & CHEMICAL RESEARCH IN TOXICOLOGY, (1998) 11/1 (54-63). ,	1-32
A	US 4 425 334 A (HUNT C ANTHONY) 10 January 1984 (1984-01-10) claims 1,6	1
X	WO 97 00236 A (KLUGER RONALD ;PAAL KRISZTINA (CA)) 3 January 1997 (1997-01-03) claims 1,11-13,15-18; examples 1,2	1-32
Y	US 5 099 012 A (MICKLE DONALD A G ET AL) 24 March 1992 (1992-03-24) column 3, line 19 - line 37; claims	1-32
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US CHEN, HAO ET AL: "Protection by vitamin E, selenium, trolox C, ascorbic acid palmitate, acetylcysteine, coenzyme Q, beta-carotene, canthaxanthin, and (+)-catechi against oxidative damage to liver slices measured by oxidized heme proteins" retrieved from STN Database accession no. 121:26809 XP002140431 abstract & FREE RADICAL BIOL. MED. (1994), 16(4), 437-44 ,	1-32

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

In Application No
PCT/CA 00/00299

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5532352	A	02-07-1996	US	5770727 A	23-06-1998
			AT	146189 T	15-12-1996
			AU	668294 B	26-04-1996
			AU	6179394 A	11-10-1994
			CA	2131455 A,C	29-09-1994
			WO	9421682 A	29-09-1994
			CN	1105800 A,B	26-07-1995
			DE	69401109 D	23-01-1997
			DE	69401109 T	28-05-1997
			DK	646130 T	02-06-1997
			EP	0646130 A	05-04-1995
			ES	2095751 T	16-02-1997
			JP	2594241 B	26-03-1997
			JP	7506123 T	06-07-1995
			NZ	262349 A	28-05-1996
WO 9956723	A	11-11-1999	AU	3696099 A	23-11-1999
US 4425334	A	10-01-1984	BR	8301713 A	13-12-1983
			CA	1197462 A	03-12-1985
			EP	0091183 A	12-10-1983
			IN	156064 A	04-05-1985
			JP	58183625 A	26-10-1983
			PH	17844 A	07-01-1985
			US	4612370 A	16-09-1986
WO 9700236	A	03-01-1997	AU	6118896 A	15-01-1997
			CA	2195005 A	03-01-1997
			EP	0785920 A	30-07-1997
			JP	10509983 T	29-09-1998
US 5099012	A	24-03-1992	NONE		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
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09/926167

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
29297-0223		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00299	20/03/2000	18/03/1999

International Patent Classification (IPC) or national classification and IPC
A61K47/48

Applicant
HEMOSOL INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/10/2000	25.05.2001

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

G. Willière

Telephone No. +49 89 2399 8548

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00299

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27	as originally filed				

Claims, No.:

1-31	as amended under Article 19				
32-38	as received on	23/04/2001	with letter of	12/04/2001	

Drawings, sheets:

1/4-4/4	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-12, 14-34, 37
	No:	Claims	1-6, 13, 35, 36 and 38
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6, 13, 35, 36 and 38
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item II

Priority

The subject-matter of the claims is not fully covered by the disclosure of the priority document (see e.g. claims 1 to 6, 35, 36 and 38). This is why the priority date for the subject-matter going beyond the subject-matter according to the priority document is the international filing date.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US-A-5 532 352 (PLIURA DIANA ET AL) 2 July 1996 (1996-07-02)

XP D2: WO 99 56723 A (HEMOSOL INC) 11 November 1999 (1999-11-11)

D3: DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL HSIA J.C. ET AL: 'Pharmacokinetic studies in the rat on a o-raffinose polymerized human hemoglobin.' retrieved from STN Database accession no. 92299803 & BIOMATERIALS, ARTIFICIAL CELLS, AND IMMOBILIZATION BIOTECHNOLOGY, (1992) 20/2-4 (587-595). ,

X D4: DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL MORDENTE A. ET AL: 'Antioxidant properties of 2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl) - 1,4-benzoquinone (idebenone).' retrieved from STN Database accession no. 1998044603 & CHEMICAL RESEARCH IN TOXICOLOGY, (1998) 11/1 (54-63). ,

Y D5: US-A-4 425 334 (HUNT C ANTHONY) 10 January 1984 (1984-01-10)

X D6: WO 97 00236 A (KLUGER RONALD ;PAAL KRISZTINA (CA)) 3 January 1997 (1997-01-03)

Y D7: US-A-5 099 012 (MICKLE DONALD A G ET AL) 24 March 1992 (1992-03-24)

D8: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US CHEN, HAO ET AL: 'Protection by vitamin E, selenium, trolox C, ascorbic acid palmitate, acetylcysteine, coenzyme Q, β-carotene, canthaxanthin, and (+)-catechi against oxidative damage to liver

slices measured by oxidized heme proteins' retrieved from STN Database accession no. 121:26809 & FREE RADICAL BIOL. MED. (1994), 16(4), 437-44.

2. The present application relates to biocompatible chemical compositions having oxygen transporting capability and comprising oxygen transporting molecules chemically bound to one or more biocompatible antioxidants selected from e.g. non-enzymatic phenolic compounds, pyrazolines, carotenoid and retinoid compounds, quinones, tetrapyrroles, indoles and aminoindoles purine analogs, ascorbic acid, and steroid and alkaloid antioxidants.
Further independent claims:
(1) a process for preparing a hemoglobin composition having antioxidant properties using inter alia polyaldehydes as crosslinking agents;
(2) use of a chemical composition as above in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients.

3. D1 refers to hemoglobin crosslinked to polyaldehyde compositions as well as to a process for preparing the same without referring to said compositions being further linked to another agent or to the use of said polyaldehyde as a crosslinking agent.

4. D2 discloses hemoglobin-haptoglobin-"hepatocyte modifying substance" complexes formed ex vivo or a hemoglobin-"hepatocyte modifying substance" complex which binds to haptoglobin in the mammalian body. Such constructs are used to deliver hepatocyte-modifying agents to the liver or other cells having the appropriate hemoglobin-haptoglobin receptor.

α-tocopherol is mentioned at page 9, line 25 to represent a hepatocyte modifying substance bound to hemoglobin. The resulting construct falls within the wording of present claims 1-6, 13 and 35, α-tocopherol representing a chromanol and thus a non-enzymatic phenolic compound (article 33(2) PCT).

5. D3 merely refers to pharmakokinetic studies on o-raffinose polymerised human hemoglobin without disclosing biocompatible chemical compositions having

oxygen transporting capability and comprising oxygen transporting molecules chemically bound to one or more biocompatible antioxidants.

6. D4 merely refers to the antioxidant properties of 2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone as such, without disclosing or suggesting an similar activity in combination with a biocompatible chemical compositions having oxygen transporting capability.

7. D5 merely discloses an oxygen transport system comprising pure crystalline hemoglobin and does not refer to biocompatible chemical compositions having oxygen transporting capability and comprising oxygen transporting molecules chemically bound to one or more biocompatible antioxidants.

8. D6 refers a multifunctional crosslinking agent without disclosing or suggesting hemoglobin in combination with a biocompatible chemical compositions having oxygen transporting capability.

9. D7 refers to chroman derivatives conjugated to either substituted (poly)saccharides, polylysines or polyornithines used in order to protect mammals from reperfusion injury.

10. D8 merely discloses the protective effect of a list of compounds (such as trolox C) against oxidative damage to liver slices.

11. It follows that the subject-matter of present claims 1-6, 13, 35, 36 and 38 lacks novelty (and thus inventive step) when compared to D2 (article 33(2) and (3) PCT).

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO99/56723	11.11.1999	30.04.1999	30.04.1998

Re Item VII

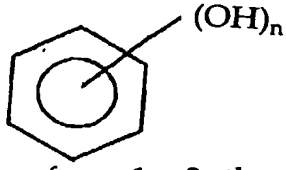
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 are not mentioned in the description, nor are these documents identified therein.

CLAIMS

1. A chemical composition having oxygen transporting capability and comprising biocompatible oxygen transporting molecules chemically bonded to one or more biocompatible antioxidants selected from non-enzymatic phenolic compounds; pyrazolines; carotenoid and retinoid compounds; quinones; tetrapyrroles; indoles and aminoindoles; purine analogs; ascorbic acid; and steroid and alkaloid antioxidants.

2. The chemical composition of claim 1 wherein the antioxidant is a phenolic compound containing one or more groups of formula:



where n is an integer from 1 - 3, the aromatic ring being optionally further substituted, and being optionally fused or linked to another carbocyclic or heterocyclic ring system.

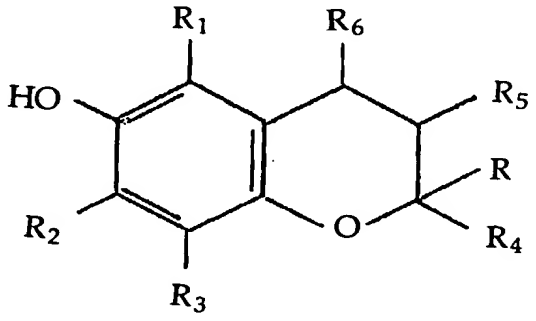
3. The chemical composition of claim 2 wherein the phenolic compound is a polyphenolic, a substituted phenolic, a phenolic ether; a di-tert.butylhydroxyphenylthio-substituted hydroxamic acid; a chroman-based compound such as a chromanol or a dihydrobenzofuranol; a flavanoid or isoflavanoid such as flavanone and dihydroflavanol; a gallate; a catechol or catechol derivative; or a phenolic acid.

4. The chemical composition of claim 3 wherein the phenolic antioxidant is a chromanol.

5. The chemical composition of any preceding claim wherein the oxygen transporting substance is a heme-protein macromolecule.

6. The chemical composition of claim 5 wherein the heme-protein macromolecule is a hemoglobin species.

7. A chemical composition according to claim 1 consisting essentially of the reaction product of an oxygen transporting compound and a 6-hydroxy chroman compound having antioxidant properties and corresponding to the general formula:



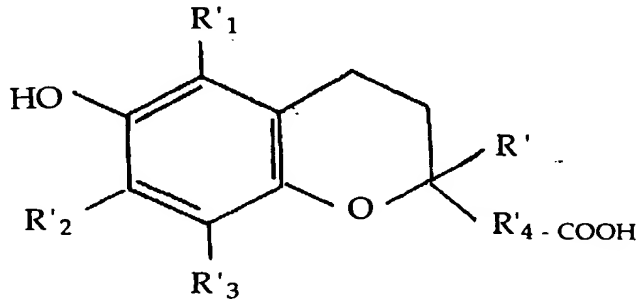
where each of R_1, R_2, and R_3, is independently selected from H, C_1 - C_8 alkyl and $(CH_2)_n X$ where n is an integer from 0 to 20; each of R_1, R_4, R_5 and R_6 is independently selected from H, C_1 - $_{20}$ alkyl, X and - $(CH_2)_m X$ where m is an integer from 0 - 20; and X is a substituent containing a reactive functional group selected in conjunction with the chosen oxygen transporting compound so as to be capable of reaction therewith to effect chemical linkage of the oxygen transporting compound to the chroman compound; with the proviso that the chroman compound includes at least one functional group X.

8. The chemical composition of claim 7 wherein the oxygen transporting macromolecule is a heme-protein macromolecule and the substituent X contains a functional group capable of reacting with amino acid residues of the protein chains of the heme protein macromoleule.

9. The composition of claim 8 wherein the heme-protein macromolecule is a hemoglobin species.

10. The composition of claim 8 or claim 9 wherein the substituent X contains a functional group selected from halo, carboxyl, amino, hydroxyl, thiol, azide, azo, aldehyde and phosphate.

11. The composition of any of claims 7 - 10 wherein the chroman compound is a chroman carboxylic acid corresponding to the general formula:



where R' is H or an alkyl radical of 1-20 carbon atoms and R'_1, R'_2 and R'_3 are independently selected from H and C_1-C_4, alkyl, and R_1, is a direct bond or C_1 - $_8$ alkyl chain.

12. The composition of claim 11 wherein the composition is a covalently linked conjugate of said chroman compound and human hemoglobin,

13. The composition of any of claims 6, 9, 10, 11 or 12 wherein the hemoglobin of the conjugate is modified by a cross-linking agent.

14. The composition of claim 13 wherein the hemoglobin is at least partially stabilized by said cross-linking agent to form stabilized tetrameric units.

15. The composition of any of claims 6 and 9 - 14 wherein the hemoglobin of the conjugate is at least partially oligomerized into oligomers of up to twelve stabilized tetrameric units.

16. The composition of any of claims 6 and 9 - 15 comprising a mixture of tetrameric stabilized hemoglobin units conjugated to the chroman carboxylic acid antioxidant and oligomers of from 2 - 8 such stabilized hemoglobin units conjugated to the chroman carboxylic acid antioxidant.

17. The composition of any of claims 13 - 16 wherein the hemoglobin is modified or cross-linked with a polyaldehyde, glutaraldehyde, a diaspirin compound, a pyridoxyl compound or a trimesoyl compound.

18. The composition of claim 17 wherein the hemoglobin is cross-linked with a polyaldehyde derived from oxidative ring-opening of a polysaccharide.

19. The composition of claim 18 wherein the polysaccharide is raffinose.

20. The composition of any of claims 6 and 13 - 19 wherein the hemoglobin-antioxidant conjugate is bonded to a biocompatible polymer.

21. The composition of claim 20 wherein the biocompatible polymer is polyethylene glycol, a polysaccharide, a polyamino acid, or an insoluble support.

22. The composition of claim 11 wherein, in the formula of the chroman carboxylic acid, at least one of R_1, R_2 and R_3 is methyl.

23. The composition of claim 22 wherein, in the formula of the chroman carboxylic acid, R_4 is a direct bond.

24. The composition of any of claims 9 - 23, wherein the chroman carboxylic acid antioxidant is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol.

25. A process of preparing a hemoglobin composition having antioxidant properties, which comprises chemically reacting hemoglobin and a hydroxy chroman compound as defined in claim 7 to form a covalently linked chemical conjugate thereof.

26. The process of claim 25 wherein, prior to conjugation to the chroman carboxylic acid, the hemoglobin is reacted with a cross-linking reagent.

27. The process of claim 25 wherein the hemoglobin-chroman carboxylic acid conjugate is subsequently reacted with a hemoglobin cross-linking reagent.

28. The process of claim 26 or claim 27 wherein the cross-linking reagent is a polyaldehyde.

29. The process of claim 28 wherein the polyaldehyde is o-raffinose.

30. The process of claim 29 wherein the hemoglobin is at least partially oligomerized by further reaction with o-raffinose

31. The process of any of claims 25 - 30 wherein the reaction between hemoglobin and the hydroxy chroman compound is conducted in the presence of an activating compound,

32. The process of claim 31 wherein the activating compound is a carbodiimide.

33. The process of claim 32 wherein the carbodiimide is 1(3-dimethylaminopropyl)-3-ethyl carbodiimide.

34. The process of any of claims 25 - 33 wherein the chroman carboxylic acid is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol.

35. Use, in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients, of a chemical composition as defined in any of claims 1 - 24.

32. The process of claim 31 wherein the activating compound is a carbodiimide.

33. The process of claim 32 wherein the carbodiimide is 1(3-dimethylaminopropyl)-3-ethyl carbodiimide.

34. The process of any of claims 25 - 33 wherein the chroman carboxylic acid is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol.

35. Use, in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients, of a chemical composition as defined in any of claims 1 - 24.

36. A composition of any of claims 1-6, wherein the non-enzymatic phenolic compound is not α-tocopherol.

37. A composition of anyone of claims 9, 10, 11,12, or 36 wherein the hemoglobin of the conjugate is modified by a cross-linking agent.

38. Use in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients of a chemical composition as defined in any one of claims 36 or 37.